Assessing the effect of threshold on graph theory metrics

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The application of graph theoretical methods in neuroscience [1] is increasingly popular, as it offers the potential to characterise and summarise the brain’s complex network. However, derived graph theory metrics are sensitive to several underlying assumptions.

To date there has been little focus on the definition of the association matrix when examining functional networks [2]. In particular, matrix connections are generally constrained to those whose connectivity exceeds an arbitrary threshold. Here we use a functional parcellation scheme to examine the effect of altering the correlation threshold (ct) (i.e. the connection density/sparsity) on common graph theory metrics. We also consider the stability of graph metrics across different time-series lengths.

### Methods

- **Data acquisition**: Eight healthy volunteers (5 male, 25-64yrs) underwent a 15 minute resting-state fMRI scan (3x3x4mm voxels, TR=2s, 450 volumes, FA = 80°).
- **Pre-processing**: Resting state fMRI data were pre-processed according to standard methodology [3].
- **Association matrix formation**: Pearson correlation coefficient was computed between BOLD timecourses extracted from all pairwise combinations of network ROIs and averaged across subjects, forming the association matrix.
- **Effect of time-series length**: Association matrices were constructed using (1) whole 15 minute time-series; (2) time-series averaged over 2 minute epochs; (3) time-series averaged over 30 second epochs.
- **Thresholding**: The association matrices were each binarised by thresholding at a range of values from ct=0.01-0.7.
- **Graph metrics**: The Brain Connectivity Toolbox [1] was used to compute graph theoretical metrics as a function of ct for each of the three time-series lengths.

### Results

- **RSN identification**: Separate cohort of 55 healthy subjects (28 male, 25-44yrs), data from 6 minute resting fMRI scans (3x3x4mm voxels, TR=2s) were used to identify resting-state networks (RSNs) using MELODIC [4].
- **ROI definition**: For each RSN, individual ROIs were defined from 3x3x3 voxel cubes centred on the maximum z-statistic voxel in each major node.

- **Correlation coefficient matrices**: Variations in the number of modules with threshold; shaded regions represent standard error across initialisations of modularity code.
- **Example of modular organisation**: Matrices are thresholded to correspond to a connection density of 0.1. Nodes are colour-coded according to degree within modules and colour coding is arbitrary.
- **Average clustering coefficient as a function of threshold**: Correlation between the thresholded matrix and the idealised version of each RSN was greatly reduced for the default mode, attention and salience networks for ct>0.35.
- **Characterise path length for each resting state network as a function of threshold**: Pearson correlation coefficient between each network is increased. As ct=0.3 the number of modules is more variable as matrix sparsity is increased. Modular organisation reveals 8 modules each representing individual RSNs (except motor and auditory which are combined in a single module, full time-series and 2 minute epochs).

### Discussion

- **The choice of connectivity threshold greatly influences graph theoretical metrics that are intended to summarise network properties. This will have a major impact on subsequent interpretation of brain networks. For pre-processing and parcellation scheme applied, the optimal correlation threshold was found to occur between 0.2 and 0.3.**
- **Graph metrics displayed stability across time-series lengths, which is particularly noteworthy when considering the application of graph theory to study sleep as data are epoched before classifying different stages.**
- **These results have strong implications for the selection of appropriate connectivity thresholds for graph analysis of RSNs, and highlight the importance of the details of the construction of the adjacency matrix.**
- **An advantage of the functional parcellation scheme employed here is that it allows some internal validation of the graph theoretical quantities, e.g. a low ct that leads to a low number of estimated modules can be identified as inappropriate. This internal validity is particularly important when considering using graph theoretical metrics to summarise changes in functional connectivity between different stages of sleep, or between patient populations and control subjects.**

### References